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E/*Z* Isomerization of 3,3-disubstituted allylic thioethers

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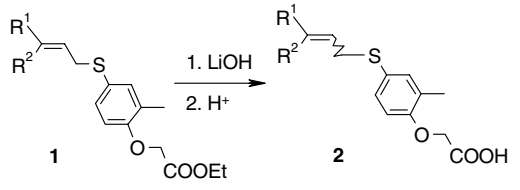
Abstract—Allylic thioethers of the general structure **1** underwent *E*/*Z* isomerization during both basic and acidic hydrolysis of the ester moiety at the remote end of the molecule. The isomerization was dependent on the substitution of the allylic moiety. The presence of a 5-membered heterocycle on the double bond supported the isomerization. However, analogous oxy-ethers were stable.

During our research on the biological activities of various allylic thioethers (**2**)[1,2] we noticed unprecedented *E*/*Z* isomerization of the double bond during hydrolysis of the remote ester group (Scheme 1).

The isomerization was first noticed during the synthesis of compound **2h**, which was prepared in order to conduct our biological study. The synthesis started from ketone **3**,[3] which was converted into alkene **4** by a Horner–Emmons reaction[4] (Scheme 2). A cross-coupling reaction[5] with thienyl stannane[6] afforded compound **5**. The predominantly formed *Z* isomer of **5** was obtained by crystallization of the mixture and the configuration was determined by NMR spectroscopy (NOE, ^{13}C, ^{1}H NMR). DIBAL-H reduction[7] led to the isomerically pure allylic alcohol **6**. The conversion of **6** to the corresponding bromide and then to the thioether[8] was, however, accompanied by *E*/*Z* isomerization. Crystallization of this mixture led to the enrichment of one isomer of **1h**. However, hydrolysis[9] of the remote ester moiety led to isomerization once again. The quantity of unwanted *E* isomer was increased after attempted crystallization from a toluene/cyclohexane mixture. On the other hand, only one isomer was detected after heating a solution of **2h** in toluene at reflux for 5 h. The ratio of isomers was determined by ^{1}H NMR spectroscopy by monitoring the vinylic hydrogen (Scheme 2).



Scheme 1. Isomerization of allylic thioethers accompanying hydrolysis of the ester group.

This phenomenon was studied further. Esters **1** and **11** were prepared from iodides **10** using a cross-coupling reaction[5] (Scheme 3). 3-Iodoallylic alcohols **9** were prepared stereoselectively by hydroalumination[10] of the corresponding propargylic alcohols.[11] Conversion into an allylic bromide or chloride followed by alkylation or direct Mitsunobu reaction of the alcohols to the corresponding thioether or ether[8] was not accompanied by isomerization of the esters **10**. Similarly, a one-pot hydroalumination–cross-coupling procedure[12] was used for the stereoselective syntheses of the allylic alcohols **14** and **15** (Scheme 4), which were the precursors for the syntheses of the *E* and the *Z* isomers of the ether analogs of compound **2h**, respectively.

All the esters were hydrolyzed;[9] the isomerization was strongly influenced by the character of the double bond substituents and the type of heteroatom at the allylic position (O vs S). Some of the thioethers were stable (Table 1) and did not undergo isomerization, while others were isomerized. Phenyl analogs were stable, whereas furyl (**2a** vs **2b**) and thienyl analogs were isomerized (**2c**,**e** vs **2d**,**f**). Heating solutions of the *E*/*Z* mixtures of these compounds did not lead to one isomer

Keywords: Allylic thioether; Allyl sulfide; *E*/*Z* Isomerization.
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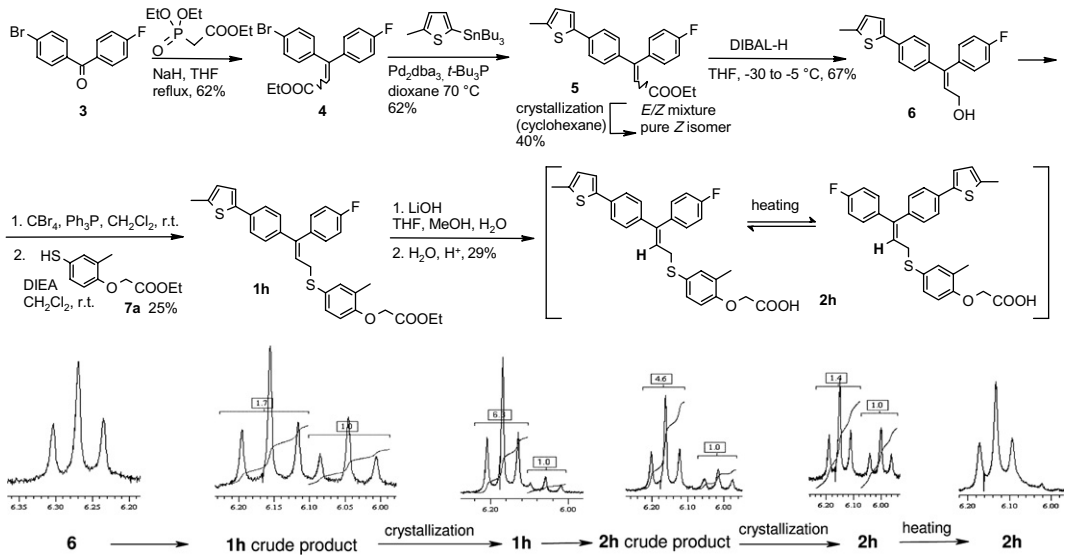
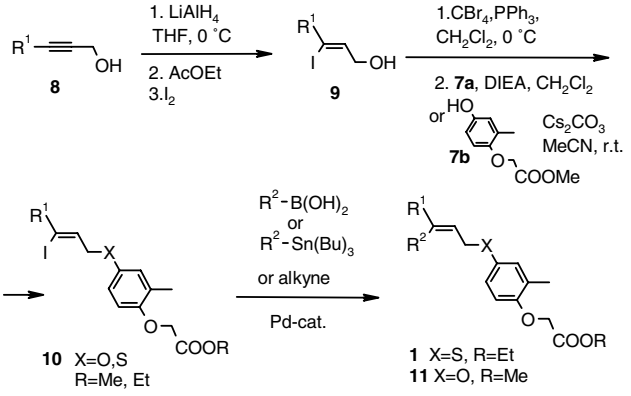


Scheme 2. Synthesis of compound **2h** and monitoring of the *E*/*Z* isomerization by ^{1}H NMR ($CDCl_3$, 300 MHz) spectroscopy. Vinyl hydrogen resonances are only shown.



Scheme 3. Stereoselective syntheses of compounds **1** and their oxy-analogs **11** (for R^1 and R^2 see Table 1).

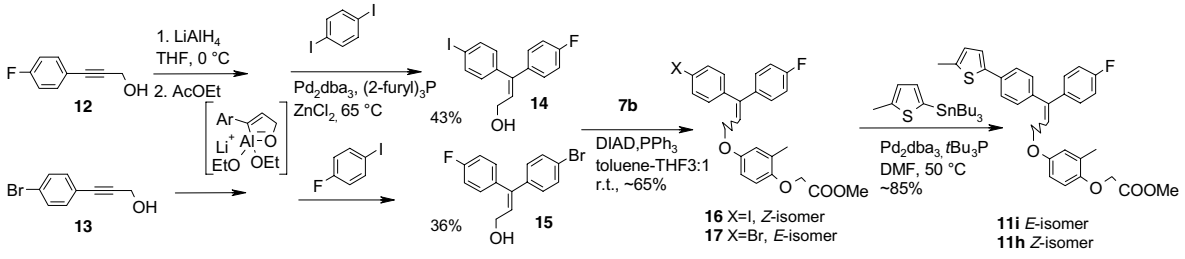
as in the case of compound **2h**. Oxy-ethers **18f–i** were however stable. The latter two compounds differed only in the configuration of the double bond, which shows that there was no *E*/*Z* isomerization equilibrium.

The isomerization was not a consequence of the basic conditions during the hydrolysis (LiOH in THF–methanol–water). When the ethyl ester was replaced with a *t*-butyl ester and the cleavage performed under acidic conditions (dilute TsOH) isomerization also occurred (Scheme 5).

We have not found any precedents for this phenomenon in the literature and the reason for its occurence is unclear. We assume that electronic effects of the carboxylic group could be transferred via the phenol system to the sulfur atom where the large d-orbitals can overlap with the double bond system. Such electronic influences together with electron-rich (5-memebered heterocyclic) substituents on the double bond may lead to isomerization.

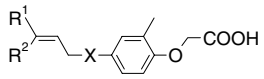
We previously reported[1] that slight changes in the substitution pattern of allylic systems with an alkyne attached to the double bond (R^2 = alkyne) led in some cases to instability of such compounds.

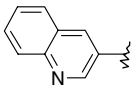
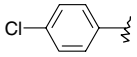
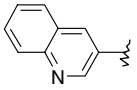
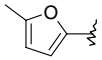
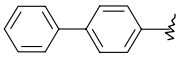
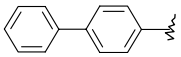
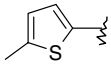
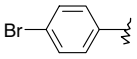
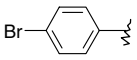
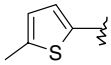
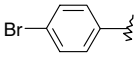
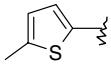
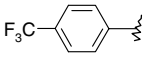
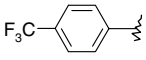
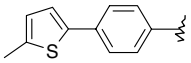
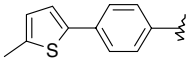
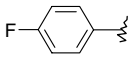
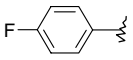
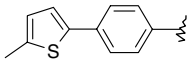
In summary, the *E*/*Z* isomerization of the allylic thioethers occurred during hydrolysis of esters **1** and depended strongly on the substituents. Oxygen analogs were stable underscoring the role of the sulfur atom.



Scheme 4. Stereoselective syntheses of oxy-analogs of **1** via one-pot hydroalumination and cross-coupling reactions.

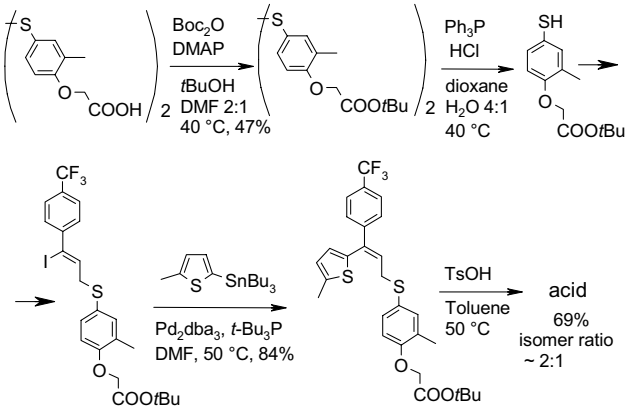
Table 1. Stability of compounds **2** and their oxy-analogs (**18**) prepared by ester hydrolysis



Acid[a]	R^1	R^2	X	*E*/*Z*	Method of preparation[b]	Yield of hydrolysis, stability (ratio of isomers)
2a			S	*E*	A	63%, stable
2b			S	*Z*	B	72%, isomerizes (1:1)
2c			S	*E*	C	36%, stable
2d			S	*Z*	B	60%, isomerizes (1:1)
2e			S	*E*	A	65%, stable
2f			S	*Z*	B	69%, isomerizes (2:1)
18f			O	*Z*	B	76%, stable
2g			S	*Z*	B	57%, isomerizes (1:1)
18g			O	*Z*	B	90%, stable
2h			S	*Z*	Scheme 2	29%, isomerizes (3:2)
18h			O	*Z*	Scheme 4	73%, stable
18i			O	*E*	Scheme 4	50%, stable

[a] *E*/*Z* Purity of esters **1**, **11** > 95% (by NMR spectroscopy), except for compound **1h**, see Scheme 2.

[b] Esters were prepared according to Schemes 2–4; transformation of iodide **10** was accomplished using the following methods: (A) arylboronic acid, Pd_2dba_3 (1.5 mol %), *t*-Bu_3P (3 mol %), Cs_2CO_3 (2 equiv), dioxane, 70–80 °C, 70–80%; (B) tributylaryltin, Pd_2dba_3 (1.5 mol %), *t*-Bu_3P (3 mol %), DMF, 50–80 °C, 50–77%; (C) byproduct of the synthesis **1e**, 23%.



Scheme 5. Synthesis of *t*-Bu protected thioethers.[13]

Acknowledgements

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References and notes

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9. General procedure for ester hydrolysis: Ester (**1**, **11**, ~0.3 mmol) was dissolved in a mixture of THF (3 mL) and MeOH (1 mL) and an aqueous solution of lithium hydroxide monohydrate (22 mg, 0.5 mmol, 1 mL) was added. The mixture was stirred for 2 h at 0 °C and then diluted with a saturated aqueous solution of ammonium chloride (20 mL). The resulting mixture was extracted with ethyl acetate (3 × 15 mL); the organic layers were combined and dried with sodium sulfate. The product was purified by column chromatography.
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13. Starting disulfide was obtained by hydrolysis of its diethyl ester, which was formed by standing a solution of **7a**[8] in THF. *t*-Bu ester formation: Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.-i.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063–1066; reduction of disulfide: Overman, L. E.; Smoot, J.; Overman, J. *Synthesis* **1974**, 59–60, The thiol was alkylated with allyl bromide in dichloromethane in the presence of DIEA under an inert atmosphere.